REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-3, 6-11, 14, 15 and 16 are in the case.

I. THE OBVIOUSNESS REJECTIONS

Claims 1-3, 6-9, 11 and 16 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bountra *et al*. (Bountra). Claims 10, 14 and 15 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bountra. Claims 1-3, 6-9, 11 and 15 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Lunardi *et al*. (Lunardi). Those rejections are respectfully traversed.

The invention as claimed in claim 1 is directed to a method of treating a patient in need of therapy for multiple sclerosis (MS). The method comprises administering to that patient a therapeutically effective dose between 500mg/day and 700mg/day of a compound of formula I wherein R^1, R^2, R^3, R^4 and R^5 are independently selected from hydrogen, trihaloalkyl and halo substituents; X^1, X^2 and X^3 are independently selected from CH, CCH_2F, CCF_3, CO alkyl, CCH_3, and nitrogen, with at least two of X^1, X^2 and X^3 being nitrogen; and Y^1 and Y^2 are independently selected from hydrogen, NH_2 and tertiary amino groups wherein the tertiary amino groups are selected from -1-piperazinyl and 4-alkyl-1-piperazinyl.

The Action again refers to page 10, lines 1-8 of Bountra, but this passage is says that, for different sodium channel blockers, the physician should take into account the age and condition of the patient. In fact, this is what the physicians did in Lunardi in treating multiple sclerosis patients 16-20 with significantly **lower** doses of lamotrigine

(i.e., 125 mg/day) than other patients (max 400mg/day). Bountra therefore urges the physician to take account of the patient's condition (multiple sclerosis) and to use a **lower** dose accordingly. Bountra clearly leads **away** from the presently claimed method of administering higher dosages in the range of 500mg/day and 700mg/day.

The Action points to claim 7 of Bountra as a disclosure that sodium channel blockers may be used to treat multiple sclerosis. However, in this regard, attention is again directed to Ramsaransing, *et al.* (of record) which indicates that carbamazepine, a sodium channel blocker, makes multiple sclerosis worse. For this further reason, one of ordinary skill would not have been motivated to arrive at the presently claimed method based on Bountra. Bountra does not give rise to a *prima facie* case of obviousness. Withdrawal of the obviousness rejections based on Bountra is respectfully requested.

Referring to Lunardi, that reference states that all of the patients had been on carbamazepine at 200 to 1500 mg/day prior to lamotrigine treatment, but that this treatment had been stopped due to serious side effects. On the contrary, Applicants has have discovered, surprisingly, that the dosage may be increased to avoid adverse effects [paragraph 0023]. These adverse effects include common occurrence of skin rash (Guberman *et al.*, Epilepsia (1999) 40(7): 985-991, page 990 Table 3 where a maintenance dose of 200-400mg is used, and Wong *et al*. (1999) Ann. Pharmacotherapy 33:1037-1042 (copies previously submitted)). These papers are directed at use of lamotrigine in regard to epilepsy, where a relatively high dose is employed as compared with other conditions. Guberman *et al.* and Wong *et al*. illustrate why a physician, in light of Bountra's disclosure to take note of the patient's

condition, would not have been motivated, as of the date of the present application, to use increased doses of lamotrigine.

In further support of the non-obviousness of the claimed dosage, attention is directed to the attached Rule 132 declaration executed by Dr. Jackie Palace (the Palace declaration). In that declaration, Dr. Palace, a physician having extensive knowledge and experience of multiple sclerosis, declares that she does not agree that patients should be prescribed lamotrigine at doses as high as 900mg. Dr. Palace bases this statement on her review of does tolerated in a recent lamotrigine trial in secondary progressive MS, where the highest tolerated dose was 300mg (average only 78mg) in this trial population. The Palace declaration observes that the maximum dose in the recent trial was 400mg which, Dr. Palace notes, was the maximum dose in the Lunardi study.

Further papers (copies previously submitted) which evidence the exercise of physician's judgment in use of **reduced** amounts of lamotrigine in treatment of multiple sclerosis are:

Leandri *et al*. (2000) J. Neurol 247:556-558 teaches doses of 25mg up to a maximum of 400mg/day;

Solaro *et al*. (2005) Neurol Sci 25: 307-310 uses 75mg/day to 400mg/day;

Silver *et al*. (2007) Journal of Pain and Symptom Management 34(4): 446-454 uses 200mg/day, 300mg/day and 400mg/day.Breur et al (2007) Clinical Therapeutics 29(9):2022-2030 teaches use of 400mg/day;

Titlie *et al*. (2008) Bratisl Lek Listy 109(9): 421-424 teaches doses of 200mg/day-250mg/day (in post stroke pain).

Based on the above, and the attached Palace declaration, it is clear that physicians, post-Bountra, would have interpreted suitable doses as **400mg/day or less**. Neither Bountra nor Lunardi suggests treatment of multiple sclerosis using the claimed dosage level of between 500mg/day and 700mg/day. Thus, taking Bountra alone (or in combination with Lunardi), the physician would **not** have been motivated to arrive at the presently claimed dosage of between 500mg/day and 700mg/day and, in fact, would have acted to reduce the dosage in the case of multiple sclerosis patients based on the state of the art. Reconsideration and withdrawal of the outstanding obviousness rejections are accordingly respectfully requested.

Favorable action on this application is awaited.

Respectfully submitted,

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